Genitourin Med 1989;65:304–307

Rheumatoid factor in congenital syphilis

MICHAEL P MEYER, ATTIES F MALAN

From the Department of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa

SUMMARY The rheumatoid factor (RF) latex test was evaluated as a test for congenital syphilis. High risk newborns of mothers with untreated or inadequately treated syphilis were studied. The asymptomatic infants were followed up for between 3 and 4 months (or longer if the VDRL test was positive). The overall performance of the RF latex test was better than that of the other tests studied, even though the sensitivity was 46·7%. The specificity and positive predictive value of the test were 100% whilst the negative predictive value was 86·4%. The test was negative in all 84 controls studied. Although a negative RF latex test cannot be used to exclude congenital syphilis in an asymptomatic infant, a positive test in the presence of maternal syphilis should lead one to strongly suspect congenital syphilis.

The increasing incidence of AIDS[1] and syphilis[2] in adults increases the risk of intra-uterine infection to the foetus. The diagnosis of both of these conditions in the newborn is problematic. The infected newborn may be asymptomatic at birth and diagnosis is then dependent on the detection of specific antibodies. However, passive transfer of maternal IgG to the foetus makes interpretation of serologic tests difficult. This necessitates prolonged follow-up to monitor antibody levels.

To overcome this problem in congenital syphilis a fluorescent treponemal antibody absorption test (FTA-Abs) for detection of IgM has been suggested.[3] Unfortunately, this test suffers from a false negative rate of at least 35% at birth.[4] Other tests based on IgM production have been proposed for the diagnosis of congenital syphilis. These include total IgM and rheumatoid factor (RF). The presence of RF in congenital syphilis was described by Lassus *et al.*[5] Subsequently RF was found in 26 of 27 infants with congenital syphilis.[6] In a recent study RF IgM was detected in three of six symptomatic infants.[7]

While RF has not been extensively studied it would appear to be of value as a test in congenital syphilis.[8] It may also be useful in other intra-uterine infections such as AIDS. The purpose of this study was to evaluate further testing for RF in congenital syphilis and to compare it with the other available tests.

Address for reprints: Dr M P Meyer, Department of Paediatrics and Child Health, University of Cape Town, Observatory 7925, Cape Town, South Africa.

Accepted for publication 20 June 1989

Methods

Patient selection

Two groups of patients were selected from the Peninsula Maternity and Neonatal Service.

Group 1: Newborns at increased risk of having congenital syphilis were studied. For inclusion into the study, their mothers had positive Venereal Disease Research Laboratory (VDRL) and Treponema Pallidum Haemagglutination (TPHA) tests and were: (1) untreated, or (2) treated in the last month of pregnancy, or (3) treated with erythromycin due to penicillin sensitivity. Many such mothers and infants came from poor socio-economic backgrounds. In order to ensure adequate follow-up, only those with a fixed, traceable address were included. Newborns who received antibiotics for reasons apart from congenital syphilis, such as amniotic fluid infection syndrome, were excluded. None of the patients studied had been included in a previous report from this hospital.[8]

Group 2: Controls. These infants and their mothers had negative serological tests for syphilis (VDRL and TPHA) at birth. The patients presented to the maternity hospital having had no prior antenatal care and the serological tests in mother and infant were part of their routine work up. Informed consent was obtained from the mothers.

Procedure at birth

The infants were examined clinically. Venous blood was drawn within 2 days of birth and allowed to clot at room temperature. The serum was either tested immediately or aliquoted and frozen at −70°C until used. The presence of RF was determined using an RF

latex slide agglutination test (Orthodiagnostics). The serum was diluted according to the manufacturers instructions (1:40), but dilutions of 1:5, 1:10 and 1:20 were also used. The dilution of 1:5 would allow detection of approximately 4 IU/ml of RF.

Total IgM was measured using a radial immunodiffusion plate (Hyland Diagnostics). The upper limit of normal for this study was regarded as 38 IU/ml (32·2 mg%).[9]

Other tests performed on all infants included the VDRL and TPHA. The FTA-Abs IgM test and radiographs of the long bones were done on all infants in Group 1. Rheumatoid factor was removed from the sera prior to performing the FTA-Abs IgM test to eliminate false positives.[10] A sheep antihuman IgG (Behring) was used for this purpose and the final serum dilution was 1:10. Cerebrospinal fluid examination was not included amongst the investigations.

Follow-up

Infants in Group 1 were examined between 4 to 6 weeks and again between 3 and 4 months. The VDRL and RF latex tests were repeated at these visits. Infants were regarded as not infected if the VDRL titre had declined to zero and the infants were well at the 3–4 month visit.[11]

The diagnosis of congenital syphilis was based on the criteria set out by Kaufman *et al.*[12] If infants fulfilled these criteria they were treated with procaine penicillin 50 000 U per kg daily for 10 days.

Results

Group 1

Sixty nine infants whose mothers had positive VDRL and TPHA tests were included in the study. Fourteen of the mothers had been treated with benzathine penicillin in the last month of pregnancy whilst five had been treated with erythromycin. The remainder had received no therapy prior to delivery.

Of the original 69, one was lost to 4 month follow-up, although when seen at 3 months the VDRL titre was declining (1:1) and the infant was clinically well. Two infants were treated by attendant doctors because of the maternal history although there were no clinical signs or serological changes compatible with congenital syphilis.

There were 15 infants with congenital syphilis. Four had definite clinical signs of congenital syphilis at birth and these infants were treated soon after delivery. A further three patients were treated early in the neonatal period. Radiological examination of the long bones revealed metaphyseal dysplasia. The three infants were born at term and appropriately grown and completely well apart from mild oedema which was present in two cases. The other eight infants with congenital syphilis were all diagnosed at follow-up.

The features which led to the diagnosis in each case, together with the results of the tests, are shown in table 1. Only one of the infected infants had a VDRL titre greater than that of the mother.

Table 1 *Clinical findings and results of laboratory investigations for infants with congenital syphilis*

	Findings at birth							*Follow-up*	
Infant No	*Clinical features*	*Radiological changes present*	*RF latex titre*	*Total IgM elevated*	*VDRL*		*FTA-Abs IgM*	*Age (weeks)*	*Remarks*
					Mother	*Infant*			
1	SGA, rash, hepatomegaly	Y	1:160	Y	1:64	1:16	+ve		Treated at birth
2	Preterm, pallor, ascites hepatosplenomegaly, pneumonia	N	1:160	Y	1:256	1:256	−ve		Died Day 1, PM findings consistent with congenital syphilis
3	Preterm, jaundice, oedema, hepatosplenomegaly	Y	−ve	Y	1:64	1:64	+ve		Treated at birth
4	Snuffles	N	1:160	Y	1:256	1:64	−ve		Treated at birth
5	Term, AGA	Y	1:80	Y	1:256	−ve	+ve		Treated early in neonatal period
6	Term, AGA	Y	1:20	Y	1:512	1:64	+ve		Treated early in neonatal period
7	Term, AGA	Y	−ve	N	1:32	1:64	−ve		Treated early in neonatal period
8	Term, AGA	N	−ve	N	1:64	1:16	−ve	18	Skin rash, snuffles, splenomegaly, VDRL 1:256
9	Term, AGA	N	−ve	N	1:32	1:2	−ve	6	VDRL 1:8
10	Term, AGA	N	1:40	N	1:64	1:16	−ve	10	Snuffles, hepatosplenomegaly, VDRL 1:64
11	Term, AGA	N	−ve	N	1:256	1:32	−ve	6	Skin rash, snuffles, VDRL 1:128
12	Preterm, SGA	N	−ve	N	1:128	1:8	−ve	14	Skin rash, snuffles, VDRL 1:256
13	Preterm, SGA	N	−ve	N	1:2	−ve	−ve	18	VDRL 1:8
14	Term, AGA	N	−ve	N	1:128	−ve	−ve	6	VDRL 1:64
15	Term, AGA	N	1:20	Y	1:128	1:16	−ve	6	Snuffles, hepatosplenomegaly, VDRL 1:64

Abbreviations: AGA—Appropriately grown for gestational age; SGA—Small for gestational age; Y—Yes; N—No; PM—Post mortem; −ve negative; +ve positive.

Table 2 *Evaluation of various tests (performed at birth) in the diagnosis of congenital syphilis*

	RF latex test	*Total IgM*	*FTA-Abs IgM*	*Radiographs of long bones*
Sensitivity (%)	46·7	46·7	26·6	33·3
Specificity (%)	100	91·7	100	100
Positive predictive value (%)	100	58·3	100	100
Negative predictive value (%)	86·4	85·2	82·3	83·6

There were 51 infants who were well at birth and who did not develop any signs of congenital syphilis during follow-up. Most of these infants had a negative VDRL test by 4 months of age, although several required follow-up for 6 months by which time the VDRL test was negative. These infants were regarded as not infected.

All of these 51 infants had a negative RF latex test (at a dilution of 1:5) and a negative FTA-Abs IgM test with normal radiographs of the long bones at birth. All 51 infants had positive treponemal tests for syphilis (TPHA or FTA-Abs IgG) at birth. Thirty one of 50 patients had positive VDRL tests (the serum of 1 patient was lipaemic). Five otherwise well infants had a serum IgM level of greater than 38 IU/ml. Serological tests for IgM against toxoplasma, rubella and cytomegalovirus (CMV) were negative.

Using these results it is possible to calculate the sensitivity, specificity and positive and negative predictive values for the various tests in the diagnosis of congenital syphilis.

The sensitivity of the RF latex test was found to be 46·7%, whilst the specificity was 100% with a positive predictive value of 100%. The negative predictive value was 86·4%.

Table 2 summarises the results obtained with the various tests.

Group 2

Eighty four controls were studied. The RF latex test was negative in all cases, whilst the total IgM was elevated in four cases. Tests of IgM antibodies to toxoplasma, rubella and CMV were negative in these four cases.

Discussion

This study compared various diagnostic tests for congenital syphilis with particular regard to the RF latex test. In three previous studies between 50 and 100% of symptomatic infants had positive RF latex tests.[6-8] We were particularly interested in the sensitivity of the test in babies at risk for congenital syphilis but without obvious clinical signs at birth. It is in this group that serological tests would be the most useful.[4] The overall sensitivity of the RF latex test was 46·7%. The sensitivity was higher in symptomatic infants (75%) compared with those without definite signs of congenital syphilis (36·4%).

The reason for the lower sensitivity in well infants in this study is unknown but it is likely that these infants were infected later in pregnancy. The absence of abnormalities on the radiographs of long bones would be in support of this (lesions usually become apparent after 5 weeks).[13] Studies in other infectious diseases have shown that the presence of RF is related to the duration of infection.[14] Thus there may have been insufficient time to mount an RF response. The sensitivity of the RF latex test was improved by performing the test at a dilution of 1:5. However, performing an enzyme-linked immunosorbent assay (ELISA) for IgM RF did not improve the sensitivity of the test (data not shown).

The specificity of the RF latex test was found to be 100%. The absence of RF in normal infants at birth has been previously established.[15] However, it is known that other congenital infections (for example rubella, cytomegalovirus) can be associated with RF production.[6 15] In general, then, the finding of a positive RF latex test may indicate a congenital infection. More specific tests will be needed to identify the responsible agent. The positive and negative predictive values of the RF latex test were high (100% and 86·4% respectively). The predictive values depend on the prevalence of disease in the population. In this study the prevalence of congenital syphilis was 22·7%. As high risk infants were selected this high prevalence is not unexpected[16] but it will influence the positive predictive value of the test.

The sensitivity of the total IgM test (46·7%) was the same as that of the RF latex test, while the positive predictive value (58·3%) was considerably lower. This is because of the presence of raised IgM levels in infants who did not have congenital syphilis. Raised IgM levels have also been detected in normal infants by other workers.[17 18]

The sensitivity of the FTA-Abs IgM test in the present study (26·2%) was lower than the quoted figure of 65% for asymptomatic infants with delayed onset disease.[4] Also, fewer patients had positive tests compared with a previous study in this hospital.[8] The reason(s) for these differences are unclear. However, subsequent to the work cited above it has become usual to prevent RF interference prior to performing

tests for specific treponemal IgM.[10 19] Rheumatoid factor may, in fact, have been responsible for some of the positive FTA-Abs IgM tests.[6] Hence RF removal may have reduced the sensitivity of the test.

Only one of the 15 infants with congenital syphilis had a VDRL titre higher than that of the mother. In addition 62% of the infants who were not infected had a positive VDRL test at birth. This means that treating all infants with a positive VDRL test may result in large numbers of uninfected infants receiving therapy and also would have missed the three infants whose VDRL tests were negative at birth.

The RF latex test was easier to carry out than the other tests studied. In addition the test was cheaper and the results were more rapidly available. Furthermore, unlike the total IgM test which should be performed within 3 days of birth, the RF latex test is still useful later in the neonatal period.[15]

However, it is obvious that none of the tests discussed have sufficient sensitivity to rule out congenital syphilis in asymptomatic infants. Other diagnostic methods including that of detecting *T. pallidum* specific IgM by Western blotting[7] are being developed. In the meantime, the finding of a positive RF latex test in the presence of maternal syphilis should lead one to strongly suspect the diagnosis of congenital syphilis.

Finally, it would seem to be worth evaluating the RF latex test in cases of perinatally acquired AIDS.

This work was supported by the Cooper-Lowveld Fund of the University of Cape Town, the Mobil Research Associateship of the Institute of Child Health and the Medical Research Council of South Africa.

The authors thank the Department of Medical Microbiology for help with the serological testing and the Superintendent at Groote Schuur Hospital for permission to conduct the study.

References

1 Centers for Disease Control. Update: Acquired immunodeficiency syndrome (AIDS)—Worldwide. *MMWR* 1988;37:286–95.

2 Centers for Disease Control. Continuing increase in infectious syphilis—United States *MMWR* 1988;37:35–38.

3 Scotti AT, Logan L. Specific IgM test in neonatal congenital syphilis. *J Pediatr* 1968;73:242–3.

4 Kaufman RE, Olansky DC, Wiesner PJ. The FTA-Abs (IgM) test for neonatal congenital syphilis: a critical review. *J Am Vener Dis Assoc* 1974;1:79–84.

5 Lassus A, Forstrom L, Piha HJ, Kustala U. Anticomplementary reactions and their relation to some auto-immune phenomena in syphilitic infection. *Acta Derm Venereol (Stockh)* 1969;49: 519–23.

6 Reimer CB, Black CM, Phillips DJ, Logan LC, Hunter EF, Pender BJ, McGrew BE. The specificity of fetal IgM. Antibody or anti-antibody? *Ann NY Acad Sci* 1975;254:77–93.

7 Dobson SRM, Taber LH, Baughn RE. Recognition of Treponema pallidum antigens by IgM and IgG antibodies in congenitally infected newborns and their mothers. *J Infect Dis* 1988;157: 903–10.

8 Meyer MP, Malan AF. Rheumatoid factor in the diagnosis of congenital syphilis. *S Afr Med J* 1987;72:668–9.

9 Malan AF. Syphilis, tetanos, tuberculose. In: Vert P, Stern L, eds. *Medicine Neonatale*. Paris: Masson, 1985.

10 Cerny EH, Farshy CE, Hunter EF, Larsen SA. Rheumatoid factor in syphilis. *J Clin Microbiol*. 1985;22:89–94.

11 Johnston NA. Neonatal congenital syphilis. Diagnosis by the absorbed fluorescent treponemal antibody (IgM) test. *Br J Vener Dis* 1972;48:464–9.

12 Kaufman RE, Jones OG, Blount JH, Wiesner PJ. Questionnaire survey of reported early congenital syphilis. Problems in diagnosis, prevention and treatment. *Sex Trans Dis* 1977;4: 135–9.

13 Ingraham NR Jr. The lag phase in early congenital osseous syphilis. *Am J Med Sci* 1936;191:819–27.

14 Bacon PA, Davidson C, Smith B. Antibodies to candida and autoantibodies in sub-acute bacterial endocarditis. *Q J Med* 1974;43:537–49.

15 Stagno S, Pass RF, Reynolds DW, Moore MA, Nahmias AJ, Alford CA. Comparative study of diagnostic procedures for congenital cytomegalovirus infection. *Pediatrics* 1980;65:251–7.

16 Larsson Y, Larsson U. Congenital syphilis in Addis Ababa. *Ethiop Med J* 1970;8:163–72.

17 Stiehm ER, Ammann AJ, Cherry JD. Elevated cord macroglobulins in the diagnosis of intrauterine infections. *N Engl J Med* 1966;275:971–7.

18 Alford CA Jr, Polt SS, Cassady GE, Straumfjord JV, Remington JS. γm-fluorescent treponemal antibody in the diagnosis of congenital syphilis. *N Engl J Med* 1969;280:1086–91.

19 Müller F, Moskophidis M, Borkhardt HL. Detection of immunoglobulin M antibodies to Treponema pallidum in a modified enzyme-linked immunosorbent assay. *Eur J Clin Microbiol* 1987;6:35–9.